K$_3$PO$_4$-catalyzed carboxylation of amines to 1,3-disubstituted ureas: A mechanistic consideration

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ABSTRACT

K$_3$PO$_4$ was found to effectively catalyze the carboxylation of amines by CO$_2$, producing corresponding 1,3-disubstituted ureas in high yields and selectivities. X-ray diffraction and FT-IR spectroscopic analysis of the solid mixture, recovered from the carboxylation of n-butylamine, revealed that K$_3$PO$_4$ was completely transformed into KH$_2$PO$_4$ and KHCO$_3$. Mechanistic and computational studies suggested that the high activity of K$_3$PO$_4$ could be attributed to the synergy effect exerted by the co-presence of KHCO$_3$ and KH$_2$PO$_4$, generated from the interaction of K$_3$PO$_4$ with CO$_2$ and water.

1. Introduction

The synthesis of 1,3-disubstituted ureas via the direct carboxylation of amines with CO$_2$ has received increasing interest with regard to the utilization of carbon dioxide, a greenhouse gas [1,2]. 1,3-Disubstituted ureas are widely used as intermediates of fine chemicals such as pesticides, herbicides, medicines, and pigments [3–9]. Recently, much effort has also been devoted to using 1,3-disubstituted ureas as precursors of isocyanates and raw materials of polyurethanes [10,11].

The most commonly used industrial process for manufacturing 1,3-disubstituted ureas is the phosgenation of amines to isocyanates followed by the reaction with corresponding amines [12–14]. However, the synthetic process involving phosgenation has inherent drawbacks such as the use of highly toxic phosgene and the generation of hydrogen chloride [15,16]. As alternative processes, oxidative and reductive carbonylation of amines have been extensively investigated [17–19], but none

of the carbonylation processes have been commercialized yet, possibly due to the failure to find inexpensive catalysts with high activity and stability. In this regard, the synthesis of 1,3-dibutylureas from carboxylation reaction of amines by CO$_2$, as shown in Scheme 1, is highly attractive in terms of economic and environmental points of view as long as suitable catalysts can be developed. A number of carboxylation catalysts have been reported, including metal salts [20], triphenylstibine oxide [21,22], N-phosphonium salts of pyridine [23,24], rare-earth metal complexes [25], sulfur trioxide–trimethylamine complex [26], dicyclohexyl carbodiimide and tertiary amine [27], and ionic liquids (ILs) [28–31]. Of these, ILs have received particular interest because some IL-based catalysts have been found to exhibit activities higher than those of other catalysts and catalytic systems.

While the advances made so far in the direct carboxylation of amines have been significant, there remains much to be improved for the practical application of the carboxylation process, particularly in terms of the activity of catalysts.
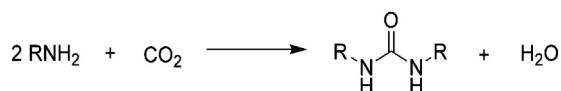
In a continuous effort to develop active catalysts for the carboxylation of amines by CO$_2$, we now report that potassium phosphate (K$_3$PO$_4$) can be used as an efficient catalyst for the carboxylation of amines. The mechanistic aspect of catalysis is also discussed on the basis of experimental and spectroscopic results.

Scheme 1. Carboxylation of amine to 1,3-disubstituted urea.

2. Experimental

2.1. General

All of the chemicals used for the synthesis of 1,3-dialkylureas were purchased from Aldrich Chemical Co. Solvents were distilled over appropriate drying agents prior to use. CO_2 with a purity of 99.9% was obtained from Shin Yang Gas Co. Korea. To remove water, all the catalysts were dried before use at elevated temperatures under vacuum.

The elemental analysis of fresh and used catalysts was made on a CHNOS Elemental Analyzer (Model: Fisons EA 1108) for C, H, and N, and on an inductively coupled plasma optical emission spectroscopy ICP-OES instrument (Varian 720/730-ES series) for P. The X-ray diffraction patterns (XRD) were recorded on a Shimadzu X-ray diffractometer (XRD-6000) using nickel-filtered Cu Kα radiation with a 2θ angle from 10° to 40°. FT-IR spectra of catalyst samples were obtained using a Nicolet FT-IR spectrometer (iS10, USA) equipped with a SMART MIRACLE accessory.

The product mixture was analyzed using an Agilent 6890 gas chromatograph (GC) equipped with an FID and a DB-5 capillary column. Product characterization was performed on a 400 MHz Bruker NMR spectrometer and on an Agilent 6890-5973 MSD GC-mass spectrometer equipped with an HP-MS capillary column.

2.2. Carboxylation of amines

A typical carboxylation reaction is as follows: n-butylamine (BuNH$_2$, 50 mmol), N-methylpyrrolidinone (NMP, 20 mL), K$_3$PO$_4$ (0.5 mmol), and toluene (2.00 g) as an internal standard were loaded into a 100 mL stainless steel bomb reactor. The reactor was pressurized with 1.0 MPa CO_2 and then heated to 170 °C with vigorous stirring. The pressure in the reactor at 170 °C was maintained at 5.0 MPa throughout the reaction using a gas reservoir equipped with a high pressure regulator and a pressure transducer. After the completion of the reaction, the product mixture was analyzed by GC. For the isolation of 1,3-dibutylurea, water (100 mL) was added to the product mixture to precipitate 1,3-dibutylurea as a white solid, which was then collected by filtration and dried in a vacuum oven overnight.

2.3. Synthesis of CO_2 adduct of K_3PO_4, $K_3PO_3(OCO_2)$

A CO_2 adduct, K$_3$PO$_3$(OCO$_2$) was prepared from the reaction of K$_3$PO$_4$ with CO_2 in NMP or CH$_3$CN at room temperature for 4 h. The same compound was also produced from the carboxylation of K$_3$PO$_4$ (2 g) conducted at 170 °C in NMP (30 mL) for 4 h in the absence of BuNH$_2$. After the reaction was completed, the solid precipitates were collected by filtration, washed with CH$_2$Cl$_2$, and then dried under a N$_2$ atmosphere at room temperature. Elemental analysis calcd. (%) for CK$_3$O$_6$P: C, 4.69; K, 45.77; O, 37.46; P, 12.09. Found: C, 4.66; K, 45.82; O, 37.41; P, 12.11. ^{31}P NMR (400 MHz, D$_2$O): δ (ppm) = 3.51, −5.08, ^{13}C NMR (400 MHz, D$_2$O): δ (ppm) = 163.91.

2.4. Quantum mechanical calculations

The carboxylation reactions of methylamine by CO_2 in the presence of K$_3$PO$_4$, KHCO$_3$, or KHCO$_3$-KH$_2$PO$_4$ were theoretically investigated using a Gaussian 03 program [32]. Methylamine was chosen as the model amine since it is the simplest system that can be used to resemble our catalytic reactions. The geometry optimizations and thermodynamic corrections were performed using hybrid Becke 3–Lee–Yang–Parr (B3LYP) exchange–correlation functional with the 6-31+G* basis sets for C, H, N, O, and P. In order to obtain the most stable geometries, all kinds of possible interaction patterns were optimized. No restrictions on symmetries were imposed on the initial structures. All stationary points were verified as minima by full calculation of the Hessian and harmonic frequency analysis.

3. Results and discussion

3.1. Carboxylation of BuNH$_2$ with CO_2

During the course of our study to develop high performance catalysts for the carboxylation of amines by CO_2, we have found that K$_3$PO$_4$ exhibits much higher activity than other alkali metal phosphates for the carboxylation of BuNH$_2$ to produce 1,3-dibutylurea. As listed in Table 1, all the alkali metal phosphates produced 1,3-dibutylurea in moderate to excellent yields when the carboxylation of BuNH$_2$ was conducted at 170 °C for 4 h. As a whole, the activity of the alkali metal phosphate increased with increasing basicity of the alkali metal phosphate [33–36]. This is reasonable because the activation of CO_2 and amines would be much easier in the presence of a more basic catalyst.

However, the significantly lower activity of K$_2$HPO$_4$ than that of KHCO$_3$, which has a similar basicity, is hard to explain by the basicity alone. It is assumed that HCO$_3^−$ is more effective than KHPO$_4^−$ in the rate-determining dehydration step of the carboxylation of BuNH$_2$ (vide infra).

The outstanding catalytic performance of K$_3$PO$_4$ was further demonstrated via a comparison of its activity with those of other active catalysts so far reported, including n-Bu$_4$PBr, [BMIm]Cl [28], 1-butyl-3-methylimidazolium hydroxide ([BMIm]OH) [30], CsOH/[BMIm]Cl [31], and Cs$_2$CO$_3$ [37]. As can be seen in Table 1, K$_3$PO$_4$ exhibited approximately 5–40% higher 1,3-dibutylurea yields when the carboxylation reactions of BuNH$_2$ were conducted under the same condition. For comparison, the activity of CaO (pK_b = 1.2) with similar basicity to K$_3$PO$_4$ (pK_b = 1.6) was also evaluated, but the yield of 1,3-dibutylurea was only 13.7%, suggesting that the basicity of a catalyst is not a sole factor in determining its carboxylation activity.
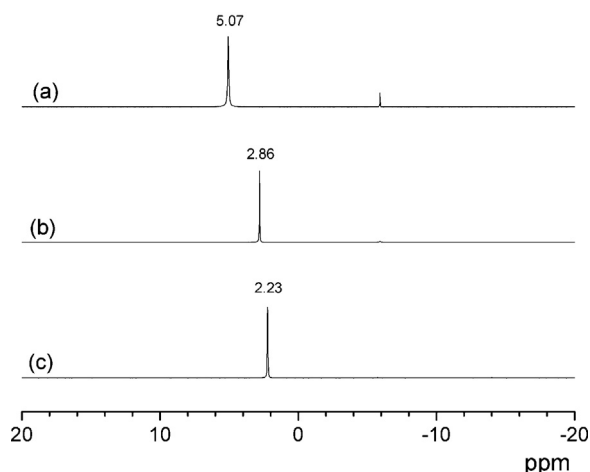
Table 1
Catalytic activities of various catalysts for the carboxylation of BuNH$_2$.[a]

Entry	Catalyst	C (%)[b]	Y (%)[c]
1	–	5.6	5.5
2	K$_3$PO$_4$	79.0	79.0
3	Na$_3$PO$_4$	63.5	63.4
4	Li$_3$PO$_4$	24.8	24.6
5	K$_2$HPO$_4$	24.5	24.4
6	KH$_2$PO$_4$	23.0	22.9
7	KHCO$_3$	64.8	64.7
8[d]	KHCO$_3$	75.5	75.5
9[e]	KHCO$_3$/KH$_2$PO$_4$	80.8	80.7
10	CsOH/[BMIm]Cl	74.3	74.3
11[f]	[BMIm]OH	40.3	40.2
12	[BMIm]Cl	43.9	43.8
13	n-Bu$_4$PBr	48.9	48.8
14	Cs$_2$CO$_3$	69.8	69.6
15	CaO	14.6	13.7

[a] Reaction condition: BuNH$_2$ (50 mmol), catalyst (0.5 mmol), NMP (20 mL), T = 170 °C, P = 5 MPa (CO$_2$), t = 4 h.
[b] C: conversion of BuNH$_2$.
[c] Y: yield of 1,3-dibutylurea.
[d] KHCO$_3$: 1.5 mmol.
[e] Molar ratio of KHCO$_3$/KH$_2$PO$_4$ = 2.
[f] [BMIm]OH: 1-butyl-3-methylimidazolium hydroxide.

Fig. 1. ^{31}P NMR spectra of (a) K_3PO_4, (b) **1**, and (c) **2** in D_2O.

3.2. Catalyst characterization

In order to obtain better insight into the catalytic nature of K_3PO_4, fresh and spent catalysts were characterized by NMR, XRD, and FT-IR spectroscopies. To this end, the carboxylation of $BuNH_2$ was performed in NMP at 170 °C and 5.0 MPa of CO_2 for 4 h with larger amounts of catalyst at a $K_3PO_4/BuNH_2$ molar ratio of 0.1. After the completion of the reaction, the solid precipitates were collected by filtration, washed with CH_2Cl_2 to remove NMP, and dried under an N_2 atmosphere at room temperature. As can be seen in Fig. 1, the ^{31}P NMR spectrum of the recovered solid (**1**) taken in D_2O is different from that of K_3PO_4, demonstrating that K_3PO_4 is transformed into other species under the experimental condition, possibly via reaction with CO_2 and water. The presence of a new singlet peak at 2.86 ppm suggests that the recovered solid, **1**, contains a phosphorous compound.

The solid **1** was also analyzed by ^{1}H NMR, but no chemical shift associated with $BuNH_2$ moiety was observed. However, in the ^{13}C NMR spectrum, a characteristic carbonate carbonyl peak was distinct at 160 ppm, indicating that the solid 1 comprises a carbonate-containing species (see Fig. S1). Based on the NMR results, it is postulated that **1** is a phosphorous compound with a carbonate group or a mixture comprising a carbonate group-containing compound and a phosphorous-containing compound. If **1** is a single phosphorous compound with a carbonate group, the most plausible structure of **1** would be $K_3PO_3(OCO_2)$ (**2**), which is a product of the reaction of strongly basic K_3PO_4 (pK_b = 1.6) with acidic CO_2 as in Eq. (1). However, XRD, FT-IR, and NMR results clearly indicate that **1** is completely different from **2** (vide infra). If **1** is a mixture comprising a carbonate group-containing compound and a phosphorous-containing compound, the most plausible carbonate species are $KHCO_3$ and K_2CO_3. Interestingly, **1** was obtained from the reaction of **2** with small amounts of water (molar ratio of water/2 = 3) at 170 °C in NMP in the absence of $BuNH_2$. The same solid **1** was also produced by the reaction of K_3PO_4 with water at 170 °C under CO_2 pressure in the absence of $BuNH_2$.

However, K_3PO_4 remained unchanged after the reaction with water at 170 °C in the absence of CO_2. This implies that **2** is produced first from the reaction of K_3PO_4 with CO_2 and then transformed into **1** by the reaction with water. It has been reported that, in the presence of water, K_3PO_4 reacts with CO_2 to produce $KHCO_3$ and K_2HPO_4 according to Eqs. (1) and (2) [38]. Therefore, it is conceivable that K_3PO_4 is converted into $KHCO_3$ and K_2HPO_4 by reaction with water generated in situ during the carboxylation of $BuNH_2$.
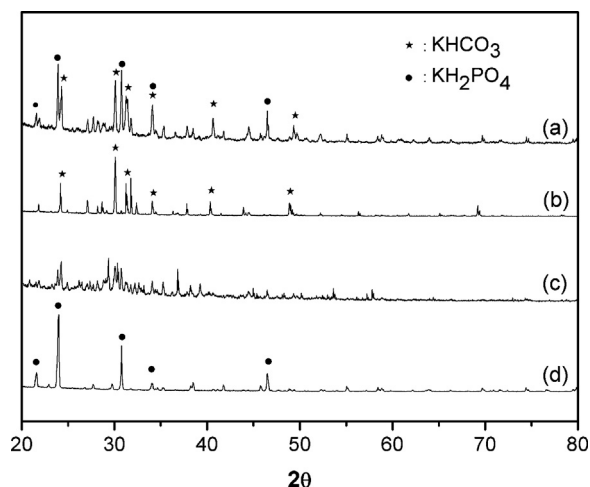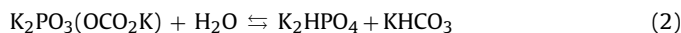
$$K_3PO_4 + CO_2 \leftrightarrows K_2PO_3(OCO_2K) \tag{1}$$

Fig. 2. XRD patterns of (a) **1**, (b) $KHCO_3$ ($\star$), (c) K_2HPO_4, and (d) KH_2PO_4 ($\bullet$). 2θ values: ($\star$) 24.2, 30.1, 31.2, 34.1, 40.4, 49.0 and ($\bullet$) 21.6, 24.0, 30.8, 34.1, 46.5.

$$K_2PO_3(OCO_2K) + H_2O \leftrightarrows K_2HPO_4 + KHCO_3 \tag{2}$$

In order to support our postulate that **1** is a mixture of $KHCO_3$ and K_2HPO_4, the XRD pattern of **1** was compared with those of $KHCO_3$ and K_2HPO_4. However, as shown in Figs. 2 and 3, the comparison of XRD patterns strongly suggests that **1** is the mixture of $KHCO_3$ and KH_2PO_4, rather than a mixture of $KHCO_3$ and K_2HPO_4. The formation of KH_2PO_4 is an indication that K_2HPO_4 was further transformed into $KHCO_3$ and KH_2PO_4 by the reaction with CO_2 and water under the carboxylation condition. The formation of KH_2PO_4 from K_2HPO_4 can be attributed to the basic property of K_2HPO_4 (pK_b = 6.8) [34]. No further transformation of KH_2PO_4 into $KHCO_3$ and H_3PO_4 was observed, presumably due to the low basicity of KH_2PO_4 (pK_b = 11.9) [38]. In fact, KH_2PO_4 was recovered unchanged after the carboxylation of $BuNH_2$ performed in NMP at 170 °C in the presence of K_2HPO_4 with a molar ratio of $K_2HPO_4/BuNH_2$ of 0.1. The formation of K_2CO_3 from the decomposition of $KHCO_3$ according to Eq. (3) is also conceivable, but XRD analysis reveals that K_2CO_3 is not produced by the decomposition of $KHCO_3$ under CO_2 pressure (see Fig. 3).
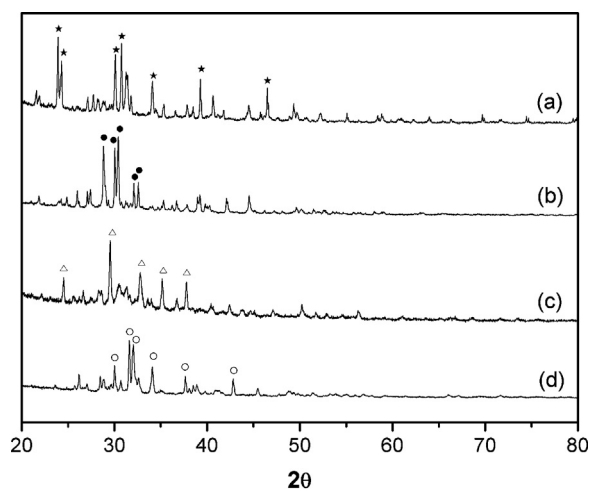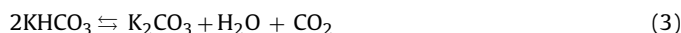
$$2KHCO_3 \leftrightarrows K_2CO_3 + H_2O + CO_2 \tag{3}$$

Fig. 3. XRD patterns of (a) **1** ($\star$), (b) **2** ($\bullet$), (c) K_3PO_4 ($\triangle$), and (d) K_2CO_3 ($\bigcirc$). 2θ values: ($\star$) 23.9, 24.2, 30.1, 30.8, 34.1, 40.4, 46.5; ($\bullet$) 28.8, 30.0, 30.4, 32.1, 32.6; ($\triangle$) 24.5, 29.5, 32.8, 35.1, 37.8; and ($\bigcirc$) 30.0, 31.6, 32.0, 34.1, 37.6, 42.8.
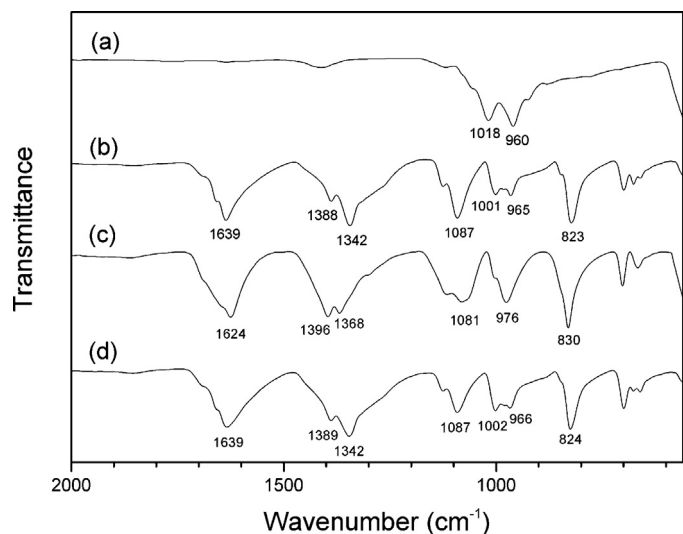
Fig. 4. FT-IR spectra of (a) K_3PO_4, (b) **1**, (c) **2**, and (d) artificial mixture of $KHCO_3$ and KH_2PO_4.

The structures of **1** and **2** were further investigated by FT-IR spectroscopy. As can be seen in Fig. 4, the FT-IR spectrum of **1** is practically the same as that of the mixture of $KHCO_3$ and KH_2PO_4 (molar ratio of $KHCO_3/KH_2PO_4 = 2$), showing absorption peaks assignable to the carbonate carbonyl, C—O—C (asymmetric carbonate) of the carbonate group, and P=O at 1639, 1342, and 1087 cm^{-1}, respectively.

3.3. Mechanistic consideration

In order to have a clue about the mechanism of the K_3PO_4-catalyzed carboxylation of amines, ^{13}C NMR experiments were conducted using D_2O as the NMR solvent to dissolve K_3PO_4. When **2** was treated with $BuNH_2$ in D_2O in a NMR tube, the carbonate carbonyl peak of **2** at 164 ppm shifted downfield to 167 ppm along with the shifts of the peaks associated with the n-butyl group (see Fig. 5). The appearance of the new carbonate carbonyl peak at 167 ppm and the presence of four carbon peaks for the n-butyl group suggest that a new species like $BuNHCO_2K$ is generated as an intermediate
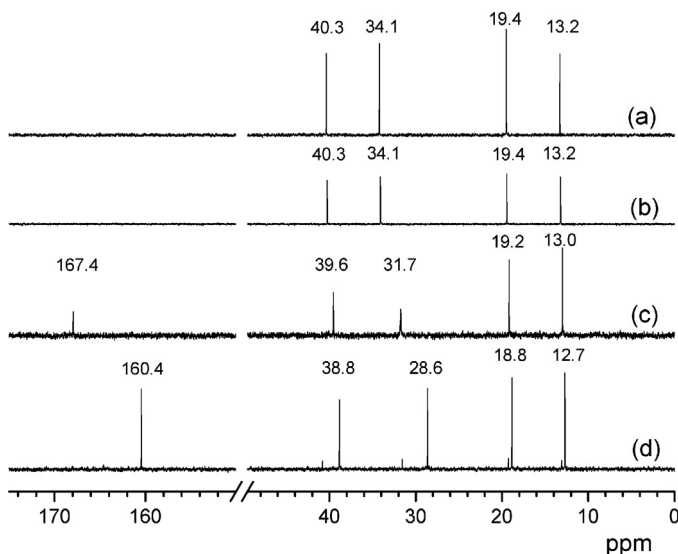

Fig. 5. ^{13}C NMR of (a) $BuNH_2$, (b) $K_3PO_4 + BuNH_2$, (c) **2** + $BuNH_2$, and (d) **2** + $BuNH_2$ + CO_2.

species. No peak shift for the butyl group was observed when $BuNH_2$ was mixed with K_3PO_4 in D_2O, implying that K_3PO_4 is capable of interacting with $BuNH_2$ only in the presence of CO_2. When a NMR tube containing a solution of **2** and $BuNH_2$ (molar ratio of $BuNH_2/2 = 2$) in D_2O was pressurized with CO_2, a new carbonate carbonyl peak appeared at 160 ppm, along with the disappearance of the carbonyl peak at 167 ppm. The appearance of the characteristic carbonate carbonyl peak at 160 ppm suggests that a carbonate species like $KDCO_3$ is generated. Considering that the number of carbon peaks is four for the butyl group, it is likely that the formation of $[BuNH_3][BuNHCO_2]$ is prohibited by the presence of the strongly basic potassium salt, **2**. The same ^{13}C NMR spectrum was also obtained from the interaction of $KHCO_3$ with $BuNH_2$ in D_2O under CO_2 pressure. This is a strong indication that $KDCO_3$ is rapidly produced from the interaction of **2** with $BuNH_2$ and CO_2 in D_2O.

On the basis of the experimental and spectroscopic results, it is assumed that the role of K_3PO_4 is 2-fold: as an initiator and as a precursor to generate $KHCO_3$ and KH_2PO_4. In fact, the mixture of $KHCO_3$ and KH_2PO_4 in a 2:1 molar ratio exhibited activity similar to that of K_3PO_4. It is worthwhile to note that the activity of $KHCO_3$ was lower than that of K_3PO_4 in the absence of KH_2PO_4, although the amount of $KHCO_3$ used was three times larger than that of K_3PO_4 on a mole basis (see Table 1). This may indicate that KH_2PO_4 plays a certain role in promoting the carboxylation of amines, most probably as a proton donor to the anionic intermediate species, because the activity of KH_2PO_4 is considerably lower than that of $KHCO_3$.

For a catalyst to be active in the carboxylation of an amine, the catalyst should possess sufficiently high basicity to accept protons from the amine and intermediate species produced in the nucleophilic addition step. Besides this, the catalyst should also exhibit high proton donating ability to the anionic intermediate species to facilitate the dehydrogenation process. In general, the proton accepting ability of the catalyst increases with increasing basicity of the catalyst, whereas the proton donating ability of a catalyst decreases with the increase of basicity of the catalyst. In other words, the proton accepting ability and proton donating ability of the catalyst are in a trade-off relation. Therefore, for the facile carboxylation of amines to 1,3-dialkylureas, it is desirable to use a base catalyst along with a proton donor as a promoter. In this context, the high activity of the catalytic system consisting of $KHCO_3$ and KH_2PO_4 could be attributed to the proton donating ability of KH_2PO_4.

Considering that $KHCO_3$ and KH_2PO_4 are the only potassium-containing species observed after the carboxylation of $BuNH_2$, it is evident that both $KHCO_3$ and KH_2PO_4 are generated from the reaction of K_3PO_4 or **2**. In the early stage of the carboxylation, K_3PO_4 seems to play a major role in catalyzing the carboxylation of $BuNH_2$, producing dibutylurea and water. K_3PO_4 starts to react with water, resulting in the formation of $KHCO_3$ and KH_2PO_4. In summary, K_3PO_4 is likely to play roles as an initiator and also as a precursor of $KHCO_3$ and KH_2PO_4 functions as a proton acceptor and a proton donor, respectively.

In the presence of a strong base (B) such as K_3PO_4 or $KHCO_3$, the first step for the carboxylation of $BuNH_2$ by CO_2 seems to occur without any difficulty according to Eq. (4).

$$RNH_2 + CO_2 + B \leftrightarrows BH^+\, RNHCO_2^- \qquad (4)$$
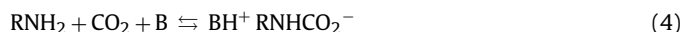
The second step would be the nucleophilic attack of the second $BuNH_2$ on the carbonyl carbon atom of $BH^+RNHCO_2^-$. For the above reaction to take place, the carbamate species $[RNHCO_2^-]$ needs to be protonated first by BH^+. The following nucleophilic attack of the second amine molecule on the carbonyl carbon of $RNHCO(OH)$ is also catalyzed by a base according to Eqs. (5) and (6).
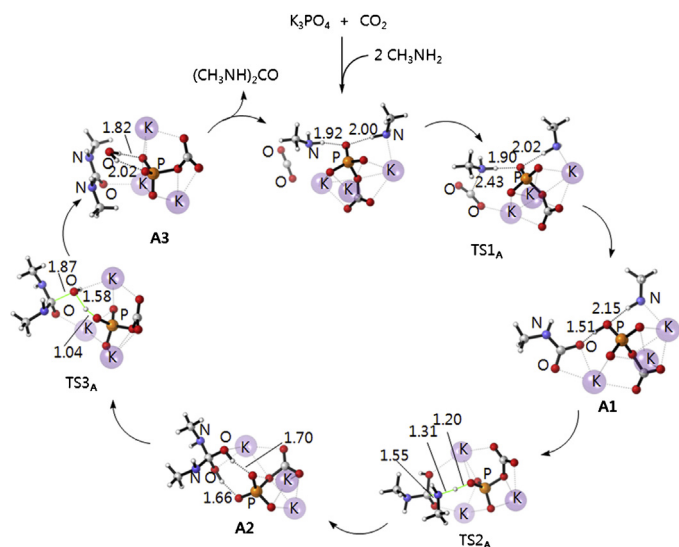
$$BH^+\, RNHCO_2^- \leftrightarrows RNHCO(OH) + B \qquad (5)$$
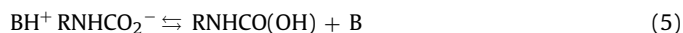
Fig. 6. Optimized structures of intermediates and transition states involved in the reaction of methylamine and CO_2 in the presence of K_3PO_4: $\Delta G^{\ddagger}_{A1} = -21.4$ kcal mol^{-1}, $\Delta G^{\ddagger}_{A2} = 10.0$ kcal mol^{-1}, $\Delta G^{\ddagger}_{A3} = 20.2$ kcal mol^{-1}, $\Delta G_{A1} = -32.6$ kcal mol^{-1}, $\Delta G_{A2} = 4.2$ kcal mol^{-1}, $\Delta G_{A3} = -22.5$ kcal mol^{-1}. The Gibbs free energy of formation (ΔG) and transition state activation energy ($\Delta G^{\ddagger}$) are relative values with respect to that of the reactant.

$$RNHCO(OH) + RNH_2 + B \leftrightarrows BH^+ RNHCO(OH)(RNH)^-$$

$$\leftrightarrows (RNH)_2C(OH)_2 + B \tag{6}$$
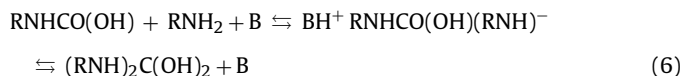
The final step would be the dehydration, as shown in Eq. (7).

$$(RNH)_2C(OH)_2 + B \leftrightarrows BH^+ (RNH)_2C(OH)O^-$$

$$\leftrightarrows (RNH)_2CO + H_2O + B \tag{7}$$
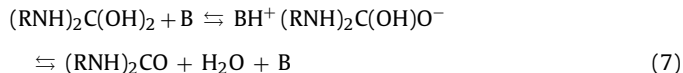
This kind of proton shuttle reaction can be accelerated, if a proton supplier like KH_2PO_4 is added to the base B. Then, instead of BH^+, KH_2PO_4 can abstract a proton from BH^+ and donate it to the anionic intermediate species, thereby providing a more facile pathway. The proton supplier of choice has to be basic enough not to protonate base B and acidic enough to protonate the reacting species.

3.4. Computational calculations

The promoting role of KH_2PO_4 for the $KHCO_3$-catalyzed carboxylation of amines was further demonstrated by the theoretical calculations. The reaction paths were calculated in vacuum. The numbers in parentheses are the energies relative to that of the reactant. For simplicity, methylamine was chosen as the model amine.

Fig. 6 shows the optimized structures of the transition states and intermediate species resulting from the interactions between CO_2 and methylamine in the presence of K_3PO_4. The calculations show that the production of dimethylurea proceeds in three steps. The first step is the interaction of CH_3NH_2 with CO_2 to form a stable carbamate intermediate species, **A1**; this step clearly shows the role of K_3PO_4 as a proton acceptor. The activation energy ($\Delta G^{\ddagger}_{A1}$) and the Gibbs free energy of formation (ΔG_{A1}) for this process were calculated to be -21.4 and -32.6 kcal mol^{-1}, respectively, demonstrating that the first step is a very facile process. The second step is the attack of methylamine on the carbonyl carbon of **A1** to form **A2**, which possesses two C—N and two O—H bonds through the transition state TS2$_{A2}$. The activation energy ($\Delta G^{\ddagger}_{A2}$) and the Gibbs free energy of formation (ΔG_{A2}) for the second step were calculated to

be 10.0 and 4.2 kcal mol^{-1}, respectively. The third rate-determining step is the proton transfer, followed by the removal of a water molecule to give the final product, **A3**. The activation energy ($\Delta G^{\ddagger}_{A3}$) and the Gibbs free energy of formation (ΔG_{A3}) for the final step were calculated to be 20.2 and -22.5 kcal mol^{-1}, respectively. Considering the favorable activation energies and the Gibbs free energies of formation, it is concluded that K_3PO_4 can be used as a highly active catalyst for the carboxylation of amines. However, as mentioned above, K_3PO_4 cannot survive in the presence of water and CO_2.

Fig. 7 shows the optimized structures of the transition states and intermediate species resulting from the interactions between CO_2 and methylamine in the presence of $KHCO_3$. The first step is the interaction of CO_2 with methylamine to produce the carbamic acid-like intermediate species, **B1**, in which one proton is located between the oxygen atoms of HCO_3^- and $CH_3NHCO_2^-$. The activation energy ($\Delta G^{\ddagger}_{B1}$) and the Gibbs free energy of formation (ΔG_{B1}) for this process were calculated to be 12.5 and -6.8 kcal mol^{-1}, respectively, indicating that the first step proceeds without much difficulty. However, unlike the carboxylation with K_3PO_4, the second step to form **B2** seems to occur with difficulty. The activation energy ($\Delta G^{\ddagger}_{B2}$) and the Gibbs free energy of formation (ΔG_{B2}) for this process were calculated to be 45.5 and 32.2 kcal mol^{-1}, respectively. The third dehydration step is also energetically unfavorable, as can be deduced from the positive values of $\Delta G^{\ddagger}_{B3}$ (48.2 kcal mol^{-1}) and ΔG_{B3} (0.9 kcal mol^{-1}), implying that $KHCO_3$ alone is not able to catalyze the carboxylation of methylamine. This is in contrast to the activity test result with $KHCO_3$, shown in Table 1. The reason for this discrepancy is not clear at the moment, but it is assumed that other species like H_2CO_3 participate as promoters in the catalysis. H_2CO_3 can be generated from the reaction of CO_2 with water produced from the non-catalytic carboxylation of methylamine.

Fig. 8 shows the optimized structures of the transition states and intermediate species for the interactions of methylamine with CO_2 in the co-presence of $KHCO_3$ as the catalyst and KH_2PO_4 as the proton donor. As can be deduced from the activity test result, the relative energies ($\Delta G^{\ddagger}_C$ and ΔG_C) of the transition states and
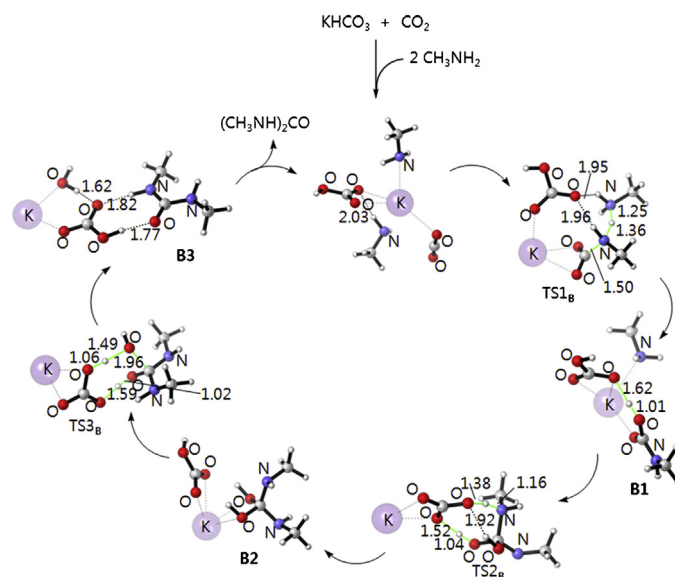

Fig. 7. Optimized structures of reaction intermediates and transition states involved in the reaction of methylamine and CO_2 in the presence of $KHCO_3$: $\Delta G^{\ddagger}_{B1} = 12.5$ kcal mol^{-1}, $\Delta G^{\ddagger}_{B2} = 45.5$ kcal mol^{-1}, $\Delta G^{\ddagger}_{B3} = 48.2$ kcal mol^{-1}, $\Delta G_{B1} = -6.8$ kcal mol^{-1}, $\Delta G_{B2} = 32.2$ kcal mol^{-1}, $\Delta G_{B3} = 0.9$ kcal mol^{-1}. The Gibbs free energy of formation (ΔG) and transition state activation energy ($\Delta G^{\ddagger}$) are relative values with respect to that of the reactant.
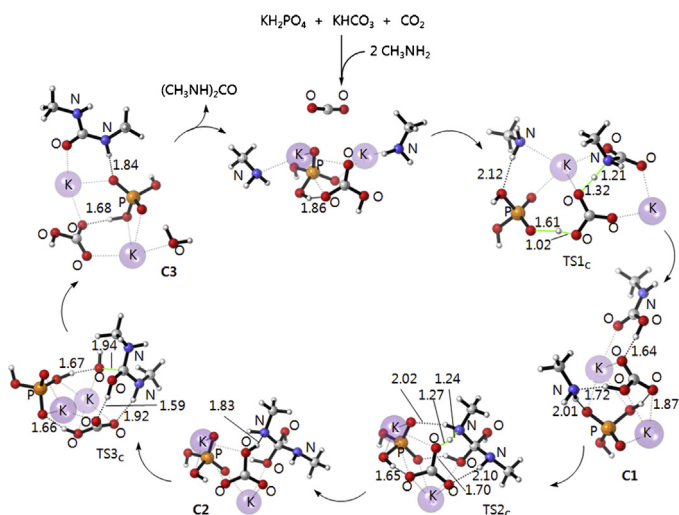
Fig. 8. Optimized structures of reaction intermediates and transition states involved in the reaction of methylamine and CO_2 in the co-presence of KH_2PO_4 and $KHCO_3$: $\Delta G^{\ddagger}_{C1} = -4.5\ kcal\ mol^{-1}$, $\Delta G^{\ddagger}_{C2} = 21.8\ kcal\ mol^{-1}$, $\Delta G^{\ddagger}_{C3} = 26.5\ kcal\ mol^{-1}$, $\Delta G_{C1} = -23.4\ kcal\ mol^{-1}$, $\Delta G_{C2} = 18.3\ kcal\ mol^{-1}$, $\Delta G_{C3} = -29.8\ kcal\ mol^{-1}$. The Gibbs free energy of formation (ΔG) and transition state activation energy ($\Delta G^{\ddagger}$) are relative values with respect to that of the reactant.

products in the co-presence of KH_2PO_4 are 15–30 kcal mol^{-1} lower than those calculated in the presence of $KHCO_3$ alone. In the first intermediate product (**C1**), the H atom of HCO_3^- interacts strongly with $H_2PO_4^-$. The second and the subsequent third step to produce the second and third intermediates, **C2** and **C3**, proceed in a fashion similar to those postulated in the presence of $KHCO_3$ only, but the activation energies ($\Delta G^{\ddagger}$) of the transition states (TS2$_C$ and TS3$_C$) are lower by 23.7 and 21.7 kcal mol^{-1}, respectively, than those of TS2$_B$ and TS3$_B$. The relative energy (ΔG) of the final product (**C3**) is calculated to be −29.8 kcal mol^{-1}, which is 30.7 kcal mol^{-1} lower than that of **B3**.

3.5. Effect of molar ratio of K_3PO_4/BuNH$_2$

Fig. 9 shows the yield of 1,3-dibutylurea as a function of the molar ratio of K_3PO_4/BuNH$_2$ at 170 °C and at 5.0 MPa of CO_2. The yield of 1,3-dibutylurea increased rapidly with the increase of the molar ratio of K_3PO_4/BuNH$_2$ up to 0.01, but increased much slowly thereafter. This could be attributed in part to the limited solubility of solid K_3PO_4 in the reaction mixture.
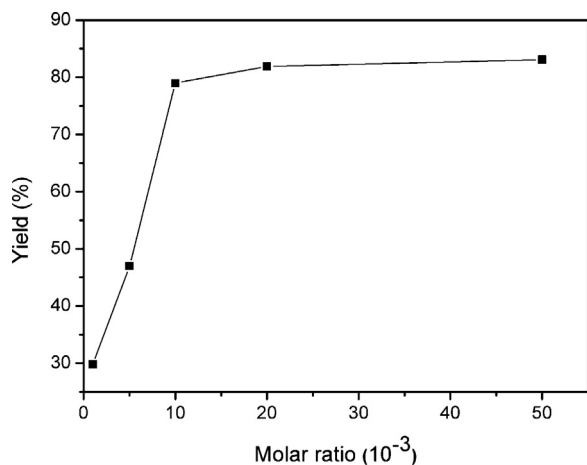

Fig. 9. Effect of K_3PO_4/BuNH$_2$ molar ratio on the yield of 1,3-dibutylurea. Conditions: BuNH$_2$ (50 mmol), NMP (20 mL), $T = 170$ °C, $P = 5$ MPa (CO_2), $t = 4$ h.

Table 2
Effect of solvent on the carboxylation of BuNH$_2$.[a]

Entry	Solvent	C (%)[b]	Y (%)[c]
1	NMP	79.0	79.0
2	DMAc	74.5	5.2
3	DMF	80.4	14.4
4	DMSO	84.4	70.5
5	CH$_3$CN	20.3	20.3
6	CH$_2$Cl$_2$	0.6	0.6
7	n-Hexane	0.3	0.3
8	CH$_3$OH	10.4	10.4
9	Isopropyl alcohol	1.6	1.6

[a] Reaction condition: BuNH$_2$ (50 mmol), K_3PO_4 (0.5 mmol), solvent (20 mL), $T = 170$ °C, $P = 5$ MPa (CO_2), $t = 4$ h.
[b] C: conversion of BuNH$_2$.
[c] Y: yield of 1,3-dibutylurea.

3.6. Effect of solvent

The K_3PO_4-catalyzed carboxylation reaction of BuNH$_2$ with CO_2 was also conducted in various solvents having different polarities. As listed in Table 2, aprotic polar solvents such as DMF, DMSO, and NMP showed considerably higher conversion of BuNH$_2$ than did other solvents. Among the aprotic polar solvents, NMP afforded the highest 1,3-dibutylurea yield. In contrast to NMP, however, DMAc and DMF were found to react with BuNH$_2$ and/or CO_2 under the experimental condition, producing numerous types of solvent-derived side products and consequently resulting in a significant reduction of the yields of 1,3-dibutylurea [27,30].

For the carboxylation of an amine to occur smoothly, the choice of solvent should be the one that can promote the nucleophilic attack, proton transfer, and dehydration processes. In this context, the use of an organic solvent with a carbonyl functional group like NMP is advantageous because the carbonyl group is capable of interacting with the hydrogen atoms of BuNH$_2$, BuNHCO(OH), and $[(BuNH)_2C(OH)_2]$, thereby assisting the nucleophilic attack of the amine and the dehydration processes.

In contrast to NMP, alcohol solvents seem to prohibit the nucleophilic attack of BuNH$_2$ on the carbonyl carbon of BuNHCO$_2$H because the alcohol solvent tends to compete with BuNH$_2$ for interaction with BuNHCO$_2$H. The importance of the solvent polarity is more evident from the results that show that the yield of 1,3-dibutylurea is negligible in nonpolar and medium polar solvents such as n-hexane and CH$_2$Cl$_2$. The ionic transition and intermediate species seem not be stabilized in these solvents.

One may suspect that the carboxylation could proceed in a homogeneous way by dissolved potassium species in NMP. To test the possibility of the homogeneous catalysis, the carboxylation of K_3PO_4 (5 mmol) was performed in NMP (20 mL) at 170 °C and 5.0 MPa of CO_2 for 2 h in a 100 mL stainless steel bomb reactor equipped with a porous metal filter, which was connected to a valve attached to the sampling port of the reactor (see Fig. S2). After the period of 2 h, the reaction mixture was filtered at 170 °C under CO_2 pressure by opening the valve connected to the metal filter and the sampling port, and the filtrate was slowly transferred to a 90 mL high pressure glass bottle (Andrews Glass Co.), which was immersed in a water bath maintained at 20 °C. The resulting transparent solution collected in the glass bottle was loaded into another 100 mL stainless steel bomb reactor containing BuNH$_2$ (50 mmol) and carboxylated at 170 °C for 2 h under 5.0 MPa of CO_2 pressure. The GC analysis of the product mixture showed that the conversion of BuNH$_2$ and the yield of 1,3-dibutylurea were 6.1 and 6.0%, respectively, which are practically the same as those obtained in the absence of a catalyst. This may indicate that the amount of dissolved potassium species in NMP under CO_2 pressure is negligible or the dissolved species is not active for the carboxylation of BuNH$_2$. In order to precisely determine the amount of dissolved potassium

Table 3
Effects of reaction temperature (T) and CO_2 pressure (P) on the carboxylation of $BuNH_2$.[a]

Entry	T (°C)	P (MPa)	Y (%)[b]
1	140	5	11.8
2	150	5	14.6
3	160	5	32.8
4	170	5	79.0
5	180	5	67.6
6	190	5	67.2
7	200	5	65.7
8	170	2	76.7
9	170	3	77.1
10	170	4	78.6
11	170	6	79.1

[a] Reaction condition: $BuNH_2$ (50 mmol), K_3PO_4 (0.5 mmol), NMP (20 mL), t = 4 h.
[b] Y: yield of 1,3-dibutylurea.

Table 4
Carboxylation of various amines by CO_2.[a]

Entry	Amine	Y (%)[b]
1	*n*-Pentylamine	84.2
2	*n*-Hexylamine	86.7
3	Benzylamine	62.0
4	Cyclohexylamine	74.6
5	*sec*-Butylamine	67.3
6	*t*-Butylamine	11.1
7	Aniline	n.r.

n.r.: no reaction.
[a] Reaction condition: amine (50 mmol), K_3PO_4 (0.5 mmol), NMP (20 mL), T = 170 °C, P = 5 MPa (CO_2), t = 4 h.
[b] Y: yield of 1,3-dialkylurea.

species, atomic absorption spectroscopic analysis (AAS) was conducted for the reaction mixture obtained from the carboxylation of $BuNH_2$ using the above filtered NMP solution. As can be deduced from the poor 1,3-dibutylurea yield of 6.0%, the potassium content was measured at below 19 ppm, suggesting that K_3PO_4 is hardly soluble in NMP under 5.0 MPa CO_2 pressure. In order to see the effect of the presence of $BuNH_2$ on the solubility of K_3PO_4 in NMP, the carboxylation of $BuNH_2$ (50 mmol) was conducted at 170 °C for 1 h under 5.0 MPa of CO_2 pressure, and the product mixture was filtered at 170 °C. The analysis of the filtrate by AAS showed that the filtrate solution contained only 24 ppm of potassium, which is about 0.26% of the potassium content used in the carboxylation. This result again indicates that the solubility of the potassium containing species in NMP under CO_2 pressure is extremely small, irrespective the presence of $BuNH_2$.

In general, the solubility of a potassium salt in an alcohol is much higher than that in NMP. Therefore, the catalytic activity of K_3PO_4 in methanol should be higher than that in NMP if the carboxylation is catalyzed homogeneously by the dissolved potassium species. However, the observed yield of 1,3-dibutylurea in methanol was only 10.4%, which is approximately 13% of that obtained in NMP (see Table 2). Although an alcohol solvent was found to give an adverse effect on the carboxylation, the yield of 10.4% in methanol is just too low for the carboxylation to be considered to proceed homogeneously by the dissolved species. This could be indirect evidence that the carboxylation of $BuNH_2$ by K_3PO_4 proceeds in a heterogeneous way.

3.7. Effects of the reaction temperature and pressure

Table 3 shows the change of the yield of 1,3-dibutylurea with temperature and CO_2 pressure for the carboxylation conducted in NMP in the presence of K_3PO_4 for 4 h. The yield of 1,3-dibutylurea increased rapidly with the temperature rise up to 170 °C, but decreased gradually on further increase of the temperature. The reason for the decrease in the yield of 1,3-dibutylurea is likely that the hydrolysis of 1,3-dibutylurea by the reaction with water to produce butylamine becomes more facilitated at temperatures higher than 170 °C. Another possible explanation is that, at higher temperatures above 170 °C, small portion of 1,3-dibutylurea decomposes into *n*-butylisocyanate, which in turn reacts with water present in the reaction mixture to produce $BuNH_2$. The selectivity of 1,3-dibutylurea was maintained at almost 100% under the experimental condition, but the decomposition of NMP was also observed above 170 °C. The formation of insoluble products derived from the butylisocyanate such as polyurea was not observed. ^{1}H NMR spectroscopy also confirmed that polyurea was not produced under the experimental condition. The carboxylation was not conducted

at temperatures higher than 200 °C because the decomposition of NMP was accelerated above 200 °C.

In contrast to the effect of temperature, the effect of CO_2 pressure on the carboxylation of $BuNH_2$ was not pronounced. When the CO_2 pressure was raised from 2.0 to 6.0 MPa at 170 °C, the yield of 1,3-dibutylurea was increased only by 2.4% from 76.7 to 79.1%.

3.8. Carboxylation of different amines

The catalytic performances of K_3PO_4 were also evaluated in NMP at 170 °C for 4 h for the carboxylation of several amines, including *n*-pentylamine, *n*-hexylamine, benzylamine, and cyclohexylamine. In all cases, as listed in Table 4, corresponding 1,3-disubstituted ureas were obtained in moderate to excellent yields. For the aliphatic primary amines, the yield of 1,3-dialkylurea increased with the increasing alkyl chain length. Since all the aliphatic primary amines tested possess similar pK_a values of around 10.6, they are expected to show similar behaviors toward the interaction with CO_2. Therefore, the different reactivity with the variation of alkyl chain length could be ascribed to the difference in dehydration reactivity of the corresponding carbamate salt. The lower yield of 62% for benzylamine could be ascribed to its lower basicity (pK_a = 9.33). Aniline, an aromatic amine, was completely inactive toward the carboxylation under the experimental condition, possibly due to its extremely low basicity (pK_a = 4.25). The yield of 1,3-dibutylurea was also affected by the steric hindrance around the nitrogen atom. Heavily hindered *t*-butylamine produced corresponding urea in a yield as low as 11.1%. It is likely that the approach of CO_2 to the amino group is restricted to a great extent by the presence of a heavily hindered *t*-butyl group. In contrast, less hindered cyclohexylamine and *sec*-butylamine gave slightly lower yields of corresponding 1,3-dialkylureas than did unhindered amines. From these results, it is concluded that both the basicity of amines and the steric hindrance around the amino groups are equally important in determining the carboxylation activity of amines.

4. Conclusions

K_3PO_4 was found to be an effective catalyst for the carboxylation of amines with CO_2, producing corresponding 1,3-dialkylureas in moderate to excellent yields. XRD and FT-IR analysis of the spent catalysts revealed that K_3PO_4 was converted into $KHCO_3$ and KH_2PO_4 during the carboxylation. Besides the catalyst, the choice of solvent is also of pivotal importance in the carboxylation of amines. The solvent used for the carboxylation should be able to stabilize the intermediate ionic species and to promote the dehydration process, without preventing the nucleophilic attack of an amine on the potassium carbamate salt. In this context, suitable solvents must possess high polarity, high thermal stability, and at least one carbonyl functional group like NMP.

Although K$_3$PO$_4$ exhibits high activity for the carboxylation of amines, further modification to enhance the catalytic activity should be made for practical application.

Acknowledgements

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.apcatb.2013.07.017.

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